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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/730,776	12/08/2003	Michael Lieberman	247332001100	5355

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MORRISON & FOERSTER LLP  
3811 VALLEY CENTRE DRIVE  
SUITE 500  
SAN DIEGO, CA 92130-2332

EXAMINER

MCGAW, MICHAEL M

ART UNIT PAPER NUMBER

1648

DATE MAILED: 10/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

10/730,776

**Applicant(s)**

LIEBERMAN ET AL.

**Examiner**

Michael M. McGaw

**Art Unit**

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 06 May 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-26 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 03/19/2004.
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_.

## DETAILED ACTION

### ***Claim Rejections - 35 USC § 112, ¶2***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 21-23 and 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for potentially enabling for a particular CpG ODN, does not reasonably provide enablement for all ODNs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection as to scope is twofold. First, enablement for CpG ODNs does not provide enablement for all ODNs. Second, enablement for a particular CpG ODN does not reasonably provide enablement for all CpG ODNs.

The activity associated with CpG ODNs cannot be extrapolated to all ODNs. The claims at issue are generally directed to immunogenic compositions containing an oligodeoxyribonucleotide (ODN) as an adjuvant combined with at least one flavivirus envelope protein. Oligodeoxyribonucleotides are simply short sequences of DNA whose length is between about 6 to about 50 or more nucleic acids. CpG ODNs are a certain class of these molecules wherein unmethylated CpG dinucleotides are flanked by two 5' purines and two 3' pyrimidines. *Spickler, A.R. et al (2003) J. Vet. Intern. Med. 17:273-281 at 278*. There are certain functional consequences associated with this sequence. CpG DNA is recognized

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as a danger signal having a direct effect on a number of different immune cell types. *McCluskie et al (2001) Current Drug Targets – Infectious Disorders, Vol. 1, No. 3: 263-271 at 265*. There is a strong predominance of Type 1-like cytokines, particularly IL-12 and IFN- $\gamma$ , with little secretion of Type-2 cytokines. While non-CpG ODNs also have an immunostimulatory effect, the immune response generated with non-CpG ODNs is quite different.

Non-CpG ODNs are then those ODNs not containing this particular motif. As a group there is no single characteristic structure (other than the absence of the CpG motif), function or response associated with a non-CpG ODN. ODNs bearing a PyNTTTGT motif have been found to stimulate B cell proliferation but not NK cell stimulation, while CpG ODNs stimulate both B-cell stimulation and NK cell stimulation. *Elias, F, et al (2003) Journal of Immunology 171:3697-3704 at 3701*. Others have reported that responses using non-CpG ODN were considerably lower than those obtained with CpG ODN and did not have the Th1 bias seen with CpG ODN. *McCluskie et al (2001) at 265*. Furthermore, "induction of the wrong type of immune response actually can enhance disease pathogenesis after the animal becomes exposed to the pathogen." *Spickler, A.R. et al (2003) at 273*. The critical point is that non-CpG ODNs are widely known to shift the immune response to a Th2-type response. (In addition to the citations above see also *Vollmer et al. (2004) Immunology 113: 212-223; Sano et al. (2003) Journal of Immunology 170 : 2376-2373*). Applicant provides on pages 5-6 of the specification:

One central paradigm that has emerged revolves around the description of two classes of T "helper" lymphocytes, termed "Th1" and "Th2" cells (Table 1). These two classes of T cells are primarily distinguished by the pattern of cytokine expression elaborated by each. The cytokines produced by Th1 cells (IFN- $\gamma$ , IL-2, TNF- $\beta$ ) tend to promote the cellular immune effector response required to combat parasitic, fungal, and intracellular viral agents (Moingeon, P., *JL Biotechnol.* (2002) 98:189-198). The cytokines produced by Th2 cells (IL-4, IL-5, IL-6, IL-10, IL-13), tend to promote antibody synthesis, i.e., the humoral immune effector response. These antibodies are effective in controlling extracellular bacterial pathogens. The balance between Th1 and Th2 cytokines is a dynamic one, because of the fact that Th1 cytokines tend to inhibit the production of Th2 cytokines *in vivo*, and vice versa. Thus, a viral vaccine capable of stimulating a "Th1" type immune response (in addition to stimulation of antibody production) would reasonably be expected to be more efficacious in protection against infection than a vaccine eliciting only an antibody response.

Two critical issues emerge from the foregoing. First, the effect of a CpG ODN cannot be extrapolated to all CpG ODNs because CpG ODNs induce a Th1 type response while non-CpG ODNs induce a Th2 response. Furthermore, applicant has only produced data showing the efficacy of certain CpG ODNs, but has no data showing the efficacy of non-CpG ODNs on the induction of cell mediated responses. (See for instance examples 2 and 4). Therefore, applicant is not enabled for non-CpG ODNs. Second, non-CpG ODNs are known to induce a Th2-type response. Such a response is the antithesis of the cell-mediated response applicant indicates as desired in the excerpted passage reproduced above. Consequently, non-CpG ODNs fail the limitation found in claim 1 wherein these compounds induce a cell-mediated immune response.

The second aspect of the scope rejection addresses the fact that enablement for a particular CpG ODN does not reasonably provide enablement

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for all CpG ODNs. It has been reported that "CpG ODN with different backbones and different sequence motifs can induce dramatically different profiles and kinetics of immune activation, and it has been suggested that several distinct families of CpG ODN exist." (See page 265, col. 1, 2<sup>nd</sup> full paragraph) Applicant indicates as much on page 26, paragraph 78 of the specification. On page 28 of the specification applicant indicates that:

ODN 10103 is far superior to either of the other two CpGs tested for stimulation of human PBMC in vivo as determined by lymphocyte proliferation assays as well as immunoglobulin synthesis (both IgG and IgM). However, CPG-A is far superior to either of the other two CpGs tested (ODN 10103 included) for stimulation of murine splenocytes in vitro as determined by lymphocyte proliferation assays (and IL-10 production', data not shown). Thus, the species specificity of these CpGs was confirmed by these experiments, and the choice of the appropriate CpG (ODN 10103) for inclusion in a vaccine formulation was made based on the results of these experiments.

On page 19 of the specification applicant lists various ODNs. None of these are designated as ODN 10103 or CpG-A. The examiner has searched the application and can find nothing that correlates the sequences claimed in claims such as claims 20, 23 or 24 with ODN 10103 or CP-A. Thus, applicant has not demonstrated that these sequences are capable of creating the Th1-type response which is associated with the induction of cell-mediated immunity. In summary, the literature indicates that not all CpG ODNs are capable of inducing the cell-mediated immune response, or are even capable of more generally enhancing the immune response along with the production of neutralizing antibody. Those skilled in the vaccine and immunotherapy art are unlikely to

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accept, without question, unsupported assertions regarding efficacy given the frequent failure experimental compositions.

Claims 1-14, 18-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being potentially enabling for a combination of a saponin such as QS-21 combined with an ODN, does not reasonably provide enablement for an ODN without a saponin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

"The result of combining adjuvants depends on the mechanism of action and toxicity of each individual component. Combinations may be better, similar to or worse than the individual components." *Spickler, A.R. et al at 278, col 2, last paragraph*. The specification provides data relating to the effect of dengue E (with or without NS1) combined with QS-21 or combined with QS-21 and CpG ODN. It does not appear that applicant has shown that CpG ODN induces a cell-mediated immune response in the absence of saponin. (See table 3 on page 24 and the last paragraph of page 25). As the quote above indicates, those skilled in the art of vaccines and immunotherapy are unlikely to accept, without question, the unsupported assertion of efficacy given the inability to determine *a priori* which particular combination of compounds will be effective. Therefore, because the specification provides no indication of the efficacy of using CpG ODNs in the absence of saponin, especially in relation to the ability to induce a cell-mediated immune response, the claims exceed the scope of that to which applicant is

enabled.

Claims 1, 2, 4, 5 and 11-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling potentially for dengue virus envelope protein subunit, does not reasonably provide enablement for other flavivirus envelope protein subunit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It is known that certain antigens induce such strong humoral responses that the adjuvant cannot influence the result. *Spickler, A.R. et al (2003) at 278*. Thus, one cannot extrapolate the immune enhancing effect of a particular adjuvant when combined with a weakly immunogenic antigen, such as dengue E, to the expectation of an enhancing effect to other flavivirus E antigens, such as yellow fever E antigen, where the antigen is more immunogenic. Thus, it is not evident, in the absence of a showing, that a a saponin and/or an ODN combined with a specific flavivirus envelope protein subunit is necessarily capable of inducing a cell-mediated immune response.

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for QS-21, does not reasonably provide enablement for other saponins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

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Applicant has provided data showing that QS-21 acts as an adjuvant when combined with dengue vaccine. QS-21 is the most extensively studied of the various saponin adjuvants, demonstrating a higher immunogenicity and lower toxicity relative other derivatives and more crude fractions such as Quil A. See *U.S. Patent No. 6,231,859 B1 to Kensil, C.A.* "[S]aponins have been shown to have different types of immune stimulating activities, including adjuvant activity." *U.S. Patent No. 6,262,029 to Press et al. at col. 3, line 65.* Again, results obtained with QS-21 cannot be extrapolated to other saponins.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4-7 and 11-17 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,416,763 B1 to McDonell et al.

Claims 1-7 and 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,432,411 to Ivy et al.

The applied references have a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it

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constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 1, 2, 4-7 and 11-17 are directed to an invention not patentably distinct from claims 1-9 of commonly assigned U.S. Patent No. 6,416,763 B1. Specifically, the '763 patent claims compositions comprising the combination of flavivirus E and NS proteins. Claim 1 of the '763 patent is as follows:

An immunogenic composition which induces an immunological response in a host subject inoculated with said composition comprising a carrier and a mixture comprising a Flavivirus truncated envelope (E) protein and a Flavivirus nonstructural (NS) protein, wherein said nonstructural protein (NS) protein has been secreted as a recombinantly produced protein, from *Drosophila* cells, and wherein the truncated envelope (E) protein comprises approximately 80%E, wherein said 80%E represents a portion of the envelope protein that comprises approximately 80% of its length starting from amino acid 1 at its N-terminus.

Column 13, line 56 teaches that the vaccine carriers can include adjuvants. Column 14, line 14 of the '763 patent teaches that it may be used with saponin adjuvants. As is indicated more fully below, the disulfide bridges (claim 5) and the dimerization of the E subunits (claim 6) is an inherent property of the E protein.

Claims 1-7 and 15-17 are directed to an invention not patentably distinct from claims 1-7 of commonly assigned U.S. Patent No. 6,432,411 to Ivy et al.

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Specifically, the '411 patent claims compositions comprising flavivirus 80% E immunogenic compositions comprising saponin adjuvants. the combination of flavivirus E and NS proteins. Claim 1 of the '411 patent is as follows:

A vaccine comprising an admixture of one or more recombinant flavivirus envelope protein subunits and an immunomodulating agent having an iscom-like structure and comprising within said iscom-like structure at least one lipid and at least one saponin, and a pharmaceutically acceptable vehicle wherein the flavivirus is a dengue virus and wherein at least one of the envelope protein subunits is a portion of the envelope protein (E) that represents the portion of the envelope protein that constitutes 80% of its length starting from amino acid residue 1 at its N-terminus to residue 395 and which portion has been secreted as or is a recombinantly produced protein from *Drosophila* cells.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent Nos. 6,416,731 B1 and 6,432,411, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C.

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102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-2, 4-6, 15-20 and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,136,561 to Ivy et al in view of U.S. Patent No. 6,544,518 B1 to Friede et al.

Applicant claims "[a]n immunogenic composition comprising, ... at least one recombinant flavivirus envelope protein subunit, wherein the envelope protein subunit is a portion of the envelope protein (E) that represents the portion of the envelope protein that constitutes 80% of its length starting from amino acid residue 1 at its N-terminus and which portion is a recombinantly produced protein from *Drosophila* cells..." combined with "an effective amount of an immunomodulating agent comprising saponin or saponin-like substance, an oligodeoxyribonucleotide, or a combination thereof..." The immunogenic composition induces the production of neutralizing antibodies and a cell-mediated immune response from a host provided with the immunogenic composition.

U.S. Patent No. 6,136,561 ('561) to Ivy et al teaches methods of preparing carboxy-terminally truncated recombinant flavivirus envelope glycoproteins employing *Drosophila melanogaster* expression systems. The '561 patent teaches, among other things, the production of E proteins of flaviviruses where the E protein is the N-terminal 80% of the protein from residue 1 to residue 395. (See claim 1) These 80% E proteins are produced in *Drosophila* cells. The '561 patent indicates that "this form is able, when administered, especially in the presence of adjuvant, to raise neutralizing antibodies in animals. Thus, this subunit represents a useful component of a vaccine for protecting subjects against dengue infection." (See column 8, line 67 to column 9, line 4). This tendency of the E protein to be somewhat weakly immunogenic is known in the art. Others have also indicated the use of E, including an 80% E protein, as an immunogen requires the addition of an adjuvant. For instance, it has been provided:

Flaviviral subunit vaccines elicit protective neutralizing antibodies in immunized animals. The level and duration of immunity elicited by such candidate vaccines in humans needs evaluation. Multiple-dose regimens of candidate subunit vaccines, perhaps in association with adjuvants and periodic booster doses, will probably be required to elicit and maintain effective anti-flavivirus immunity. Kinney, R.M. et al. (2001) Intervirology 44:176-197.

Thus, it is clear that (1) it an inherent property of flaviviral subunit vaccines is that they induce the production of neutralizing antibody and (2) one using an recombinant E protein in an immunogenic composition would seek an appropriate adjuvant or combination thereof. A protein expressed in such a system would form the disulfide bridges as indicated in claim 5 and associate into dimmers as indicated in claim 6. (See also page 12 of the specification)

U.S. Patent No. 6,544,518 B1 ('518) to Friede et al. teaches adjuvants for vaccines. The '518 patent related to the use of saponin and an immunostimulatory oligonucleotide as an adjuvant to antigen-based vaccines. (see abstract) Importantly, '518 patent points out "that immunostimulatory oligonucleotides (CpG) and saponin combinations are extremely potent adjuvants." (column 2, line 55) Furthermore, "saponin and oligonucleotides in the adjuvant and vaccine compositions act synergistically in the induction of antigen specific antibody and are potent in the induction of immune responses conventionally associated with the Th1-type immune system." (column 2, lines 60-65) Thus, the addition of saponin and immunostimulatory oligonucleotides to the recombinant E protein, as taught by the '561 patent, would create an immunogenic composition that induces the production of neutralizing antibodies and a cell-mediated immune response from a host. As for the use of flavivirus antigen, this was clearly contemplated by the '518 patent. Claim 9 of the '518 patent was directed at an immunogenic composition (comprising QS21 and an immunostimulatory oligonucleotide) where the antigen is derived from Dengue virus.

One of ordinary skill in the art would have been motivated to add the adjuvant composition of the '518 patent (U.S. Patent No. 6,544,518 B1) to the recombinant E protein, as taught by the '561 (U.S. Patent No. 6,136,561) because the recombinant E protein, as taught by the '561 patent is known to be somewhat weakly immunogenic and the '561 patent indicates that its immunogenicity can be enhanced through the addition of an adjuvant. One of

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ordinary skill in the art would have expected to achieve a more immunogenic composition by including saponin and an immunostimulatory oligonucleotide because the '518 patent teaches the efficacy of such combinations. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

As to claims 19 and 20, applicant's SEQ ID NO:1 appears to meet the limitations of claim 19. SEQ ID NO: 1, as found in claim 20, is identical to SEQ ID NO:1 as taught in the '518 patent. (See sequence listing in the patent immediately below column 28). Thus, the '518 patent teaches the limitations as found in claims 18-20. As to claim 24, this is the sequence that is recognized to be the most active hexamer in murine models. (See Hartmann et al. cited by applicant on form 1449). As to claims 25 and 26, one would use the composition in a pharmaceutically acceptable carrier, in a therapeutically acceptable manner and in a therapeutically effective amount.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,136,561 to Ivy et al in view of U.S. Patent No. 6,544,518 B1 to Friede et al. as applied to claims 1-2, 4-6, 15-20 and 25-26 above, and further in view of Kinney, R.M. et al. (2001)

U.S. Patent No. 6,136,561 indicates that immunity to one serotype of dengue does not confer immunity to other serotypes of dengue. (col. 2, line 2) *Kinney, R.M. et al. (2001) Intervirology 44:176-197* indicates that a vaccine a tetravalent vaccine against all four dengue strains is required to provide protection against all four serotypes of the virus. (See for instance the abstract).

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4-7, 11-17 and 25-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,416,763 B1 to McDonell et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '763 patent claims the use of immunogenic compositions comprising E and NS1 while additionally teaching that such compositions can further include an adjuvant, including saponin.

Specifically, the '763 patent claims compositions comprising the combination of flavivirus E and NS proteins. Claim 1 of the '763 patent is as follows:

An immunogenic composition which induces an immunological response in a host subject inoculated with said composition comprising a carrier and a mixture comprising a Flavivirus truncated envelope (E) protein and a Flavivirus nonstructural (NS) protein, wherein said nonstructural protein

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(NS) protein has been secreted as a recombinantly produced protein, from *Drosophila* cells, and wherein the truncated envelope (E) protein comprises approximately 80%E, wherein said 80%E represents a portion of the envelope protein that comprises approximately 80% of its length starting from amino acid 1 at its N-terminus.

Column 13, line 56 teaches that the vaccine carriers can include adjuvants. Column 14, line 14 of the '763 patent teaches that it may be used with saponin adjuvants. As is indicated more fully below, the disulfide bridges (claim 5) and the dimerization of the E subunits (claim 6) is an inherent property of the E protein.

Claims 1-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,749,857 B1 to Peters et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '857 patent teaches/claims recombinant dimeric envelope vaccines against flaviviral infection of immunogenic compositions where the compositions further include an adjuvant.

Claims 1-7 and 15-17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,432,411 to Ivy et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '411 patent teaches a vaccine that contains at least one *Drosophila* cell-secreted, recombinantly-produced form of a truncated Flavivirus envelope glycoprotein, as an active ingredient, and an adjuvant, as a critical component of the vaccine. The

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composition includes at least one saponin, and a pharmaceutically acceptable vehicle. Such a vaccine protects a subject against infection by a Flavivirus.

**Conclusion**

Currently all claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number is (571) 272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

m.m.

Monday, October 18, 2004

*Mary E. Mosher*  
MARY E. MOSHER  
PRIMARY EXAMINER  
GROUP 1800 1600